Clinical trial results:
A multi-centre randomised, double-blind, placebo-controlled trial of pre-hospital treatment with tranexamic acid for severely injured patients at risk of acute traumatic coagulopathy.

Summary

EudraCT number	2019-004118-33
Trial protocol	DE
Global end of trial date	14 June 2023

Results information

Result version number	v1 (current)
This version publication date	07 October 2023
First version publication date	07 October 2023
Summary attachment (see zip file)	ClinicalStudy Report (20230418_PATCH_Synospe_ClinicalStudyReport_final.pdf)

Trial information

Trial identification

Sponsor protocol code	PATCH_Trauma

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02187120
WHO universal trial number (UTN)	U1111-1169-6738

Notes:

Sponsors

Sponsor organisation name	University Witten/Herdecke
Sponsor organisation address	Alfred-Herrhausen-Str. 50, Witten, Germany, D-58448
Public contact	IFOM, Institut für Forschung in der Operativen Medizin, 0049 02219895726, patch@uni-wh.de
Scientific contact	IFOM, Institut für Forschung in der Operativen Medizin, 0049 02219895726, patch@uni-wh.de

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	20 December 2022
Is this the analysis of the primary completion data?	Yes
Primary completion date	20 December 2022
Global end of trial reached?	Yes
Global end of trial date	14 June 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To determine the effect of early administration of TXA, compared to placebo, on mortality and favourable outcomes (moderate disability or good recovery) at six months in severely injured adults at risk of ATC who are treated in advanced trauma systems.
To determine the effect of early administration of TXA, compared to placebo, on coagulation and fibrinolysis, and on clinical outcomes that are mediated through other putative inflammatory, immune, and neurological effects of plasmin.
To determine whether early administration of TXA, compared to placebo, is associated with excessive vascular occlusive events, especially among potentially higher risk patients (eg >50 years old).

Protection of trial subjects:

Upon arrival at the scene of injury, EMS clinicians will follow usual resuscitation protocols to address immediate life-threatening conditions of the airway, breathing or circulation.

Review and consider any protocol modifications or ancillary studies proposed by the study investigators after the main trial begins to ensure that these do not negatively impact on the main trial. Protocol modifications will be considered in the context of their potential impact on scientific integrity and subject safety;

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2020
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Germany: 8
Country: Number of subjects enrolled	Australia: 1299
Worldwide total number of subjects	1307
EEA total number of subjects	8

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0

Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	1307
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Adult patients (age ≥18 years);
• Injured through any mechanism;
• COAST score ≥3;
• First dose of study drug can be administered within three hours of injury; and
• Patients to be transported to a participating trauma centre

Pre-assignment

Screening details:

Upon arrival at the scene of injury, EMS clinicians trained in study procedures decided whether the patient is eligible for inclusion in the trial. Patients assessed as meeting the inclusion criteria at any time during the prehospital period, with no exclusion criteria, were randomised.

Period 1

Period 1 title	Overall Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

All trial personnel and participants will be blinded to treatment allocation. An independent pharmaceutical packaging company will be responsible for labelling ampoules containing TXA or sodium chloride (placebo) and preparing trial packs. The independent pharmaceutical packaging will contain the study code to determine which patients received TXA or placebo and this will not be available to trial investigators until completion of the trial.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

As soon as possible after injury, EMS clinicians administered a 10 ml ampoule containing 0.9 % w/v Sodium Chloride via iv injection (ampoules containing Sodium Chloride appear identical to ampoules containing TXA). After the patient arrived at hospital,
clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

Arm type	Placebo
Investigational medicinal product name	sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

0.9% sodium chloride;
Mode of administration: slow intravenous injection and infused intravenously;
pre-hospital administration of tranexamic acid followed by an infusion over 8 hours

Arm title	Experimental intervention - TXA

Arm description:

As soon as possible after injury, emergency medical services (EMS)
clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

Arm type	Experimental

Investigational medicinal product name	TXA
Investigational medicinal product code	
Other name	Cyclokapron
Pharmaceutical forms	Injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

1g TXA (in 10 ml water) and 1g TXA (in 1000 ml 0.9 % NaCl);
Mode of administration: slow intravenous injection and infused intravenously;
after injury, emergency medical services (EMS) clinicians administered 1 g Tranexamic Acid;
After the patient arrived at hospital, clinicians administered 1 g TXA

Number of subjects in period 1	Placebo	Experimental intervention - TXA
Started	646	661
Completed	559	572
Not completed	87	89
Consent withdrawn by subject	26	31
Lost to follow-up	61	58

Baseline characteristics

Reporting groups

Reporting group title	Overall Period

Reporting group description: -

Reporting group values	Overall Period	Total	
Number of subjects	1307	1307	
Age categorical Units: Subjects			
Adults (18-64 years)	1307	1307	
Age continuous Units: years			
arithmetic mean	44.15		
standard deviation	± 19.3	-	
Gender categorical Units: Subjects			
Male	918	918	
female	382	382	
Not recorded	7	7	

Subject analysis sets

Subject analysis set title	Primary outcomes - extended GOS-E
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consist of all randomised patients. Dichotomised Glasgow Outcome Scale Extended (GOSE) at 6 months: A favourable outcome is
defined as GOSE scores 5-8 (moderate disability or good recovery) as opposed to GOSE scores 1-4 (died=1, severe disability 2-4).

The binary primary outcome of favourable GOSE (scores 5-8) was compared between treatment groups using a risk ratio together with a 95% confidence interval and p-value, estimated by a logbinomial regression model. If model convergence was not achieved, then Poisson regression with robust standard errors was applied.

Subject analysis set title	Primary outcomes - extended GOS-E
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population will consist of all randomised patients with the exception of those who did not receive both doses of study drug or received open label TXA or did not meet the inclusion/exclusion criteria: age <18 years, had a COAST score <3, received their study drug >3 hours after injury, were pregnant, were residents at an aged care facility or did not attend a participating study centre.

Subject analysis set title	Secondary outcomes -24h
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

Subject analysis set title	Secondary outcomes -28 days
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Mortality at:
• 24 hours;
• 28 days;
• 6 months.

Subject analysis set title	Secondary outcomes -6month
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Mortality at:
• 24 hours;
• 28 days;
• 6 months.

Reporting group values	Primary outcomes - extended GOS-E	Primary outcomes - extended GOS-E	Secondary outcomes -24h
Number of subjects	1300	847	1300
Age categorical Units: Subjects			
Adults (18-64 years)	1307	847	1307
Age continuous Units: years			
arithmetic mean	44.15	44.75	44.15
standard deviation	± 19.3	± 18.85	± 19.3
Gender categorical Units: Subjects			
Male	918	602	918
female	382	245	382
Not recorded			

Reporting group values	Secondary outcomes -28 days	Secondary outcomes -6month	
Number of subjects	1300	1300	
Age categorical Units: Subjects			
Adults (18-64 years)	1307	1307	
Age continuous Units: years			
arithmetic mean	44.15	44.15	
standard deviation	± 19.3	± 19.3	
Gender categorical Units: Subjects			
Male	918	918	
female	382	382	
Not recorded			

End points

End points reporting groups

Reporting group title	Placebo

Reporting group description:

As soon as possible after injury, EMS clinicians administered a 10 ml ampoule containing 0.9 % w/v Sodium Chloride via iv injection (ampoules containing Sodium Chloride appear identical to ampoules containing TXA). After the patient arrived at hospital,
clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

Reporting group title	Experimental intervention - TXA

Reporting group description:

As soon as possible after injury, emergency medical services (EMS)
clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

Subject analysis set title	Primary outcomes - extended GOS-E
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population consist of all randomised patients. Dichotomised Glasgow Outcome Scale Extended (GOSE) at 6 months: A favourable outcome is
defined as GOSE scores 5-8 (moderate disability or good recovery) as opposed to GOSE scores 1-4 (died=1, severe disability 2-4).

The binary primary outcome of favourable GOSE (scores 5-8) was compared between treatment groups using a risk ratio together with a 95% confidence interval and p-value, estimated by a logbinomial regression model. If model convergence was not achieved, then Poisson regression with robust standard errors was applied.

Subject analysis set title	Primary outcomes - extended GOS-E
Subject analysis set type	Per protocol

Subject analysis set description:

The PP population will consist of all randomised patients with the exception of those who did not receive both doses of study drug or received open label TXA or did not meet the inclusion/exclusion criteria: age <18 years, had a COAST score <3, received their study drug >3 hours after injury, were pregnant, were residents at an aged care facility or did not attend a participating study centre.

Subject analysis set title	Secondary outcomes -24h
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

Subject analysis set title	Secondary outcomes -28 days
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

Subject analysis set title	Secondary outcomes -6month
Subject analysis set type	Intention-to-treat

Subject analysis set description:

Mortality at:
- 24 hours;
- 28 days;
- 6 months.

Primary: GOS-E	
End point title	GOS-E
End point description:	

End point type	Primary
End point timeframe:	
6 month	

End point values	Placebo	Experimental intervention - TXA	Primary outcomes - extended GOS-E	Primary outcomes - extended GOS-E
Subject group type	Reporting group	Reporting group	Subject analysis set	Subject analysis set
Number of subjects analysed	559	572	1131	727
Units: Subject	646	661	1300	1300

Statistical analyses

Statistical analysis title	Primary outcome analysis – favourable 6-month GOSE
Comparison groups	Placebo v Experimental intervention - TXA
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.95
Method	log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	1
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.9
upper limit	1.12
Variability estimate	Standard deviation

Secondary: Death within 24hr	
End point title	Death within 24hr
End point description:	

End point type	Secondary
End point timeframe:	
24 hours after injury	

End point values	Placebo	Experimental intervention - TXA	Secondary outcomes -24h	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	559	572	1297	
Units: Subject	643	657	1300	

Statistical analyses

Statistical analysis title	secondary endpoint analyses - 24hr
Comparison groups	Placebo v Experimental intervention - TXA
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	other
Method	log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.69
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.51
upper limit	0.94
Variability estimate	Standard deviation

Secondary: Death within 28 days

End point title	Death within 28 days
End point description:	
End point type	Secondary
End point timeframe:	
28 days after injury	

End point values	Placebo	Experimental intervention - TXA	Secondary outcomes -28 days	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	559	572	1290	
Units: Subject	643	657	1300	

Statistical analyses

Statistical analysis title	secondary endpoint analyses - 28 days
Comparison groups	Placebo v Experimental intervention - TXA
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	other
Method	log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.79
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.63
upper limit	0.99

Secondary: Death within 6 month

End point title	Death within 6 month
End point description:	
End point type	Secondary
End point timeframe: death by 6 month after injury	

End point values	Placebo	Experimental intervention - TXA	Secondary outcomes - 6month	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	559	572	1277	
Units: Subject	643	657	1300	

Statistical analyses

Statistical analysis title	secondary endpoint analyses - 6 month
Comparison groups	Placebo v Experimental intervention - TXA
Number of subjects included in analysis	1131
Analysis specification	Pre-specified
Analysis type	other
Method	log-binomial regression
Parameter estimate	Risk ratio (RR)
Point estimate	0.83

Confidence interval	
level	95 %
sides	2-sided
lower limit	0.67
upper limit	1.03

Adverse events

Adverse events information

Timeframe for reporting adverse events:

overal period: 6 month
July 2014 - March 2021

Adverse event reporting additional description:

Any untoward medical occurrence in study participant which does not necessarily have to have a causal relationship with the study drug, but which was of concern to the organisation/site principal investigator's clinical judgement. Ae´s in this study included (but were not limited to) vascular occlusive events, seizures, cardiac arrest, anaphylax

Assessment type	Systematic

Dictionary used

Dictionary name	CPMP/ICH/377/95
Dictionary version	July 2000

Reporting groups

Reporting group title	Placebo

Reporting group description:

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clinicians administered a second 10 ml ampoule containing 0.9 % w/v Sodium Chloride added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

Reporting group title	Experimental intervention - TXA

Reporting group description:

As soon as possible after injury, emergency medical services (EMS) clinicians administered 1 g Tranexamic Acid (TXA; 10 ml ampoule containing 100 mg/ml TXA in water for injection) via iv injection. After the patient arrived at hospital, clinicians administered 1 g TXA (10 ml ampoule containing 100 mg/ml TXA in water for injection) added to up to 1 litre 0.9 % w/v Sodium Chloride infused iv over 8 h.

Serious adverse events	Placebo	Experimental intervention - TXA	
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 643 (0.62%)	3 / 657 (0.46%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Complication of procedure			
subjects affected / exposed	1 / 643 (0.16%)	0 / 657 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardiac arrest			

subjects affected / exposed	2 / 643 (0.31%)	2 / 657 (0.30%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Heparin-induced thrombocytopenia (HITS)			
subjects affected / exposed	1 / 643 (0.16%)	0 / 657 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Respiratory failure			
subjects affected / exposed	0 / 643 (0.00%)	1 / 657 (0.15%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	Experimental intervention - TXA	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 643 (1.24%)	16 / 657 (2.44%)	
Injury, poisoning and procedural complications			
Others			
subjects affected / exposed	8 / 643 (1.24%)	16 / 657 (2.44%)	
occurrences (all)	19	25	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/3731424